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COLONIC STRICTURES IN PATIENTS WITH CYSTIC FIBROSIS: RESULTS OF A SURVEY OF 114 CYSTIC FIBROSIS CARE CENTERS IN THE UNITED STATES

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Abstract:

We describe fifteen reports of stricture of the colon requiring surgery in cystic fibrosis patients identified from a survey of 114 Cystic Fibrosis Care Centers in the United States. Ages ranged from two to seven years and seven of the fifteen reports were female. A history of meconium ileus was reported in nine of the fifteen reports. Fibrosis of the submucosa was described in fourteen of fifteen surgical pathology reports. Pancreatic enzyme use history was available from fourteen reports. All had taken delayed-release products containing microtablets for six to forty-six months at doses ranging from 6,900 to 29,000 units lipase/kg per meal, but only eight of fifteen patients used such products labeled as containing greater than 20,000 units lipase/capsule immediately prior to surgery.

Key words: cystic fibrosis, pancreatic enzymes, colonic strictures.

INTRODUCTION

Distal intestinal obstruction syndrome (DIOS) occurs in two percent of cystic fibrosis (CF) patients per year and is characterized by recurrent colicky abdominal pain, right lower quadrant mass and signs of intestinal obstruction [1,2]. The signs and symptoms of the syndrome are usually attributed to complete or partial obstruction of the intestinal lumen in the ileocecal area by inspissated material, however other abdominal pathology (ie., Crohn's Disease, intussusception, appendiceal abscess) can mimic DIOS. Stricture of the ascending colon had not been previously described in the differential diagnosis of DIOS until Smyth et al. reported five such cases[3]. Subsequent to Smyth's report similar cases were reported from the United Kingdom, Ireland and Denmark [4,5,6,7,8]. Each case had been switched to high-strength pancreatic enzymes (HSPE), preparations labeled as containing 22,000-25,000 units of lipase per capsule, prior to the development of a colonic stricture with submucosal fibrosis. A survey, administered by the Cystic Fibrosis Foundation (CFF) in the United States, was conducted to search for similar cases of colonic stricture and to describe the use of pancreatic enzymes prior to surgery on the colon.

METHODS

For 26 years, the Cystic Fibrosis Foundation has maintained a CF

patient registry. In 1993 the total patients registered numbered 19,505 patients (comprising 80% of the diagnosed CF population in the United States) seen in 114 CF Care Centers. In January of 1994, in conjunction with the Food and Drug Administration (FDA) a survey questionnaire was sent to 114 CF Care Centers requesting a description of any cases of stricture or obstructive bowel disease not responding to conservative treatment within the past three years. Data requested included: age, gender, use of supplemental pancreatic enzymes, other drug therapies, surgical and pathology reports, and significant past medical history.

Each report was reviewed to determine whether it met the following working case definition: symptoms consistent with intestinal obstruction that failed to respond to medical management and subsequently resulted in surgical excision of a segment of strictured colon. The reporters of the identified cases were contacted if additional information was needed.

Pancreatic enzyme products were categorized as follows: immediate release products; delayed-release products containing enteric coated microspheres with a labeled content of 4000 to 12,000 units of lipase per capsule; and delayed-release products containing enteric coated microtablets with a labeled content of 4,000 to 30,000 units of lipase per capsule. Average daily dose per product category was calculated by adding the average monthly prescribed doses in units lipase/kg per meal and dividing such

sum by the total number of months used for that particular product category. The pancreactic enzyme products also contain protease and amylase. Labeled lipase content was used only to categorize these products and was not meant to incriminate that component.

SURVEY RESULTS

Forty-five reports were received from 113 of 114 surveyed CF Care Centers. Fifteen of the forty-five reports met our case definition. Eleven CF Centers located throughout the United States were responsible for the fifteen reports. All were single case reports with the exception of three reporters reporting three two, and two cases, respectively. Two reports had diagnostic studies consistent with a stricture of the colon but surgery had not yet been done.

Selected characteristics of the fifteen patients from the survey, as well as cases reported in the literature, are summarized in Table 1.

The portion of the colon excised included the right colon in seven cases, the transverse colon in five cases and almost the entire colon in three cases. Surgical pathology reports were available for all cases. On gross examination the colonic wall was frequently described as thickened with luminal narrowing at

the stricture site. Descriptions of the mucosal surface included atrophy with loss of rugal folds and four reporters noted a "cobblestone" appearance of the mucosa. With the exception of one case, all described fibrosis of the submucosa, with two noting fatty infiltration of the submucosa. Non-specific inflammation was described in seven reports and two reports described an increase in eosinophils in the lamina propria. Ganglion cells and nerve trunks were reported to appear normal in four cases. Three reporters noted the presence of chylous ascites at surgery.

Pancreatic enzyme usage histories were available for fourteen patients (Table 2). Total duration of use of any delayed-release product containing microtablets ranged from six to forty-six months with a mean of twenty-one months. Average dose of any delayed-release product containing microtablets ranged from 6,900 to 29,000 units lipase/kg per meal.

DISCUSSION

The fifteen cases of colonic stricture requiring surgery were remarkable for being on average younger (mean 4.2 years) compared to all CF patients reported to the CF National Patient Registry (mean 14.8 years) and consistent with the ages of the fifteen cases reported in the literature. Meconium ileus or perinatal surgery was reported in five of the fifteen (33%) cases reported in the literature compared to nine of fifteen (60%) from the CFF

survey. Of the nine CFF survey cases with a history of meconium ileus, seven cases were reported to have required surgical intervention. Briars has suggested that stricture formation could be related to a compromise of the colonic arterial supply resulting from a perinatal illness requiring surgical intervention[6].

The gender distribution of the cases reported to the CFF survey was 46% female, identical to the percentage of females among all CF patients reported to the registry, but higher than the percentage among the cases reported in the literature, 33% female.

Colonic stricture cases reported from the CFF survey have many characteristics in common with the cases initially reported by Smyth, including a similar histologic picture. Smyth noted that all their patients had been switched to HSPE preparations 12-15 months previously and Smyth raised the hypothesis that the development of these strictures may be related to the introduction of (HSPE) preparations[3]. In contrast, only eight of the CFF survey cases were reported to be using a delayed-release product containing microtablets with a labeled content of more than 20,000 units of lipase per capsule immediately prior to surgery. However, the CFF surveyed cases all had used a delayed-release formulation containing microtablets prior to surgery suggesting that intensity of dosing and duration of therapy may

be important risk factors as well. In comparison to the six cases reported by Knabe who were taking HSPE doses of 25,000-75,000 units lipase/kg per meal the CFF survey cases were taking delayed-release products containing microtablets at doses ranging from 6,800 to 29,000 units lipase/kg per meal. Knabe suggests that higher doses taken by their patients may be related to the more widespread involvement of the colon in their cases[4]. Among the three cases reported from the CFF survey who had almost their entire colon excised, average microtablet formulation doses were 8,100, 9,800, and 17,800 units lipase/kg per meal, respectively.

In response to the foreign and domestic reports of colonic stricture in cystic fibrosis patients, the FDA met with the three firms who market these products in the United States. As a result, McNeil Pharmaceutical, Scandipharm, Inc. and Solvay Pharmaceticals, Inc. voluntarily withdrew from the market their HSPE products (Pancrease, Ultrase, and Creon, respectively) labeled as containing more than 20,000 units of lipase activity effective within 60 days of a Dear Doctor letter, dated February 11, 1994 and signed by all three firms. The letter was sent to all United States Cystic Fibrosis Centers as well as other physicians targeted as likely to prescribe these products. In addition, the letter was published in the *Journal of the American Medical Association*, the *New England Journal of Medicine* and *Pediatrics* in their April 13, April 14 and April issues, respectively. In the letter the manufacturers recommended that

patients be maintained on the lowest daily dosage of pancreatic enzymes necessary to minimize steatorrhea and maintain good nutritional status. This survey was initiated while those actions were ongoing.

Conclusions concerning the relationship between use of delayed-release pancreatic enzymes containing microtablets and stricture of the colon can not be drawn from these case series. More detailed information on enzyme use in CF patients, the characteristics of the CF patients and the manufacturing specifics of the formulations involved in the cases are needed. The proportion of patients seen at CF Care Centers taking similar high amounts of lipase units per meal but not presenting with colonic stricture cannot be determined from this survey. The cases described from the CFF survey represent those with the most severe strictures of the colon requiring surgery and therefore do not include cases with earlier stages of stricture, nor do they preclude the possibility that other sites in the gastrointestinal tract may be involved. Further investigations are needed to determine the etiology of these strictures.

The possibility of stricture needs to be considered in all patients taking large doses of pancreatic enzymes containing microtablets who have symptoms of intestinal obstruction. Physicians and other health-care practioners who are aware of additional suspected cases are encouraged to report them to FDA's

MEDWatch program[9]. To facilitate reporting, adverse event forms are available in several publications including the *Physicians' Desk Reference*, the *FDA Medical Bulletin*, and the *American Medical Association's Drug Evaluations*.

Table 1. Selected characteristics of reported colonic stricture cases				
Source	N	Age(s)	Sex	Meconium ileus*
CFF Survey	15	2-7	8M, 7F	9
Smyth et al.[3]	5	2-13	5M	1
Oades et al.[4]	1	3	M	
Campbell et al.[5]	1	7	F	1
Briars et al.[6]	1	4	M	1
Mahony et al.[7]†	1	9	M	1
Knabe et al.[8]‡	6	2-11	2M, 4F	1

* history of meconium ileus or perinatal surgery
† non-operated
‡ 5 of 6 non-operated

TABLE 2.
PANCREATIC ENZYME USE UNTIL TIME OF SURGERY
Duration of use in months (order of use)
Average dose in units lipase/kg per meal

Case No.	Immed. Release	Delayed Release Micro-spheres	Delayed Release Micro-tablets 4-12	Delayed Release Micro-tablets 16-20	Delayed Release Micro-tablets 24-30	Average Dose Micro-tablets
1.		23 (1) 1,400		37 (2) 11,500		11,500
2.		18 (1) 9,500	19 (2) 14,100	8 (3) 20,900		16,100
3.		72 (1) 4,000		24 (2) 17,800		17,800
4.		34 (1) 4,300		40 (2) 8,000	6 (3) 18,000	9,300
5.		12 (1) 9,700		18 (2) 20,500		20,500
6.	5 (2) 2,500			9 (1) 29,100		29,100
7.				12 (1) 9,600	6 (2) 10,000	9,700
8.		13 (1) 4,400	6 (2) 14,300	10 (3) 9,100		11,000
9.				2 (1) 4,700	9 (2) 8,900	8,100
10.					6 (1) 9,800	9,800
11.		1 (1) 3,600	9 (2) 6,700	3 (3) 14,200	2 (4) 17,000	9,800
12.					13 (1) 14,300	14,300
13.	33 (3) 7,400		7 (1) 700	5 (2) 4,100	20 (4) 9,800	6,900
14.					18 (1) 17,000	17,000

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